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| 10/588,070 | 12/13/2006 | Roger C. Adami | PC25670A | 5146 |

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PATENT DEPARTMENT, MS8260-1611
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| EXAMINER | |
|---|---|
| JAGOE, DONNA A | |
| ART UNIT | PAPER NUMBER |
| 1614 | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

~IPGSGro@pfizer.com

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/588,070 | ADAMI ET AL. | |
| | Examiner | Art Unit | |
| | Donna Jagoe | 1614 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *11-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/13/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

***Claims 11-27 are presented for examination.***

### *Priority*

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. § 120, for U.S. Provisional Application Number 60/540,897, filed January 30, 2004 and under § 365(c) to PCT IB05/000100 filed January 17, 2005 is acknowledged.

### *Claim Rejections - 35 USC § 112 (1st Paragraph)*

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 11-27 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

To be enabling, the specification of the patent application must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557, 1561 (Fed. Cir. 1993). Explaining what is meant by "undue experimentation," the Federal Circuit has stated that:

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. PPG v. Guardian, 75 F.3d 1558, 1564 (Fed. Cir. 1996).[1]

The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth by *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 wherein, citing *Ex parte Forman*, 230 USPQ 546 (Bd. Apls. 1986) at 547 the court recited eight factors:

1) the quantity of experimentation necessary,
2) the amount of direction or guidance provided,
3) the presence or absence of working examples,
4) the nature of the invention,
5) the state of the prior art,
6) the relative skill of those in the art,
7) the predictability of the art, and
8) the breadth of the claims.

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. *In re Fisher*, 57 CCPA 1099, 1108, 427 F.2d 833, 839, 166 USPQ 18, 24 (1970). Keeping that in mind, the *Wands* factors are relevant to the instant fact situation for the following reasons:

1. <u>The nature of the invention, state and predictability of the art, and relative skill of those in the art</u>

[1] As pointed out by the court in *In re Angstadt*, 537 F.2d 498 at 504 (CCPA 1976), the key word is "undue", not "experimentation".

The invention relates to a composition comprising a therapeutically effective amount of an active ingredient, β-cyclodextrin and preservative, wherein the active ingredient is a compound of formula I and further drawn to a method of treating a disease for which a neurokinin receptor (NK-1) antagonist is indicated in mammals. However, it is noted that the instant specification, at page 10, lines 31-32 defines treating or treat to embrace "**preventative and prophylactic treatment**".

The relative skill of those in the art is high, generally that of a formulation chemist with an advanced degree.

That factor is outweighed, however, by the unpredictable nature of the art. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 166 USPQ 18, at 24 (In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved.), *Nationwide Chemical Corporation, et al. v. Wright, et al.*, 192 USPQ 95 (one skilled in chemical and biological arts cannot always reasonably predict how different chemical compounds and elements might behave under varying circumstances), *Ex parte Sudilovsky* 21 USPQ2d 1702 (Appellant's invention concerns a pharmaceutical activity. Because there is no evidence of record of analogous activity for similar compounds, the art is relatively unpredictable) *In re Wright* 27 USPQ2d 1510 (the physiological activity of RNA viruses was sufficiently

unpredictable that success in developing specific avian recombinant virus vaccine was uncertain).

Hesketh et al. (Jan. 1999, Journal of Clinical Oncology Vol. 17, No. 1 pages 338-343), cited for evidentiary purposes, teach NK-1 receptor antagonists produced antiemetic activity after administration of cisplatin was 64% of patients receiving the NK-1 receptor antagonist CJ-11,974 (page 341, column 1, *Efficacy*). This reference plainly demonstrates that there is a great deal of unpredictability with regard to prevention of emesis when the NK-1 antagonist is administered to patients.

2. The breadth of the claims

The specification that supports the claims is extremely broad insofar as it discloses the prevention or prophylactic use of NK-1 receptor antagonists for a disease.

3. The amount of direction or guidance provided and the presence or absence of working examples

The specification provides no direction or guidance for determining the particular administration regimens with regard to differing diseases or with regard to prevention vs. treatment (*e.g.*, dosages, timing, administration routes, etc.) necessary to fully appreciate the scope or breadth of the claims. There are no working examples that demonstrate prevention of any condition in the specification.

4. The quantity of experimentation necessary

Because of the known unpredictability of the art associated with NK-1 receptor antagonists (as discussed *supra*) and in the absence of experimental evidence commensurate in scope with the claims, the skilled artisan would not accept the assertion that the instantly claimed combination could be predictably prevent or prophylax against a disease as inferred in the claims and contemplated by the specification.

*Genentech Inc. vs. Nova Nordisk* states, "[A] patent is not a hunting license. It is not a reward for a search but a compensation for its successful conclusion and 'patent protection' is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable" (42 USPQ 2d 1001, Fed. Circuit 1997).

In the instant case, Applicants have presented a that a therapeutic dose of the NK-1 receptor antagonists represented by instant claims 11-27 prevent a disease. There is one specific use recited for these NK-1 receptor antagonists, noted on page 43 of the instant specification, for the treatment of emesis or improving anesthesia recovery in mammals. However, the claims are not limited to any specific disease, dosage or formulation. As such, it is entirely speculative that administration of any NK-1 receptor antagonist embraced by the limitations of formula I could prevent or prophylax any disease that is treatable by NK-1 receptor antagonists.

Accordingly, the instant claims do not comply with the enablement requirement of 35 U.S.C. § 112, first paragraph, since to practice the claimed invention a person of

ordinary skill in the art would have to engage in undue experimentation, with no assurance of success.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 12-27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 12 recites the limitation "a pharmaceutical composition according to claim 1" in line 1 of the claim. There is insufficient antecedent basis for this limitation in the claim because claim 1 has been cancelled.

Claim 14 recites the limitation "the pharmaceutical composition according to claim 12 wherein the preservative is…" in line 1 of the claim. There is insufficient antecedent basis for this limitation in the claim because there is not a preservative recited in claim 12 from which claim 14 depends.

Regarding claim 17, it recites "the composition of claim 15 wherein about 1mg/ml to about 5 mg/ml of the preservative is unsequestered in the cyclodextrin. This is confusing because claim 15 recites the composition comprising about 2.5 mg/ml of meta-cresol. The amount that is unsequestered in the composition of instant claim 17

exceeds the amount that is contained in the composition of instant claim 15 from which it depends.

Claim 21 provides for the use of a composition, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claims 13-16, 18-20 and 22-27 are indefinite to the extent that they read on the rejected base claims.

***Claim Rejections - 35 USC § 101***

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claim 21 is rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

One interpretation of instant claim 21 is “a method of use" claim. In order to advance prosecution in this case, claim 21 will be interpreted as a “**method of use**” claim.

Claim 21 is rejected under 35 U.S.C. 101 because the claimed invention is directed to both a "process" of use and a “process of making”. The claim embraces or overlaps two different statutory classes of invention set forth in 35 U.S.C. 101 which is drafted so as to set forth the statutory classes of invention in the alternative only. *Ex parte Lyell*, 17 USPQ2d 1548 (Bd. Pat. App. & Inter. 1990) *Id.* at 1551.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claim 11 is rejected under 35 U.S.C. 102(e) as being anticipated by Giles-Komar et al. U.S. Patent No. 7,163,681 B2.

Giles-Komar et al. teach a pharmaceutical composition comprising a therapeutically active agent (anti-integrin antibodies) a beta cyclodextrin such as 2-hydroxypropyl β cyclodextrin (column 43, lines 11-12) and other pharmaceutical excipients or additives that are suitable for use (column 43, lines 18-28) and further comprising a preservative such as m-cresol. (column 44, lines 24-35).

Claims 12-14 and 20-24 are rejected under 35 U.S.C. 102(e) as being anticipated by Bronk et al. US Patent Application Publication No. 2003/0139443 A1.

Bronk et al. teach tachykinin antagonists (NK-1 receptor antagonists) encompassed by the limitations of instant claim 12 (see page 4) wherein R2 is isopropyl (0098), R2 is *tert*-butyl (0099), R2 is methyl (0100), R2 is ethyl (0101) and wherein R2 is *sec*-butyl (103) and further comprising propylene glycol (paragraph 149 and 150) and sulfobutyl ether β cyclodextrin (see example 1, page 7, paragraph 163). Regarding treatment of a disease for which a neurokinin receptor antagonist is indicated, Bronk et al. teach that these NK-1 receptor antagonists are useful for treatment of abnormal anxiety behavior in companion animals (see abstract) such as dogs (paragraph 11).

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 15-19 and 25-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Giles-Komar et al. U.S. Patent No. 7,163,681 B2 and Bronk et al. US Patent Application Publication No. 2003/0139443 A1. as applied to claims 11-14 and 20-24 above, and further in view of Ono et al. Eur. J. Pharm. Sci. 1999 (U).

Giles-Komar et al. teach a pharmaceutical composition comprising a therapeutically active agent and a β cyclodextrin such as 2-hydroxypropyl β cyclodextrin (column 43, lines 11-12) and other pharmaceutical excipients or additives that are suitable for use (column 43, lines 18-28) and further comprising a preservative such as m-cresol. (column 44, lines 24-35). Bronk et al. teach tachykinin antagonists (NK-1 receptor antagonists) encompassed by the limitations of instant claim 12 (see page 4) wherein R2 is isopropyl (0098), R2 is *tert*-butyl (0099), R2 is methyl (0100), R2 is ethyl (0101) and wherein R2 is *sec*-butyl (103) and further comprising propylene glycol (addressing instant claim 14) (paragraph 149 and 150) and sulfobutyl ether β cyclodextrin (see example 1, page 7, paragraph 163). Regarding treatment of a

disease for which a neurokinin receptor antagonist is indicated, Bronk et al. teach that these NK-1 receptor antagonists are useful for treatment of abnormal anxiety behavior in companion animals (see abstract) such as dogs (paragraph 11).

It does not teach the composition with the active compound of claim 12 that is preserved with meta-cresol specifically. Giles-Komar et al. teach a β-cyclodextrin composition with an active agent that is preserved with m-cresol (meta-cresol) and Bronk et al. teach the specific compound in a cyclodextrin composition with a different preservative. Claims 15-19 are drawn to a specific amount of meta-cresol preservative in the β cyclodextrin composition and the specific binding value indicating the amount of preservative that is unsequestered. Ono et al. teach the formula by which one having ordinary skill in the art could readily calculate such binding values (see pages 135-136).

I would have been obvious to employ the composition of formula I with a preservative such as m-cresol and a β cyclodextrin motivated by the teaching of Giles-Komar et al. who teaches a successful combination of β-cyclodextrin and m-cresol and Bronk et al. who discloses a formulation with the compound of formula I of instant claim 12 combined with sulfobutyl ether β cyclodextrin and a preservative, armed with the formula of Ono to assure that the correct amount of β cyclodextrin is employed so as to prevent inclusion complexes and ensure solubility, stability and bioavailability (page 133, column 1). Addressing instant claims 25-27, methods of using the NK-1 receptor antagonists are disclosed in Bronk et al. for the treatment of abnormal anxiety behavior in companion animals such as dogs (a mammal) in view of the obviousness rejection supra.

Thus the claims fail to patentably distinguish over the state of the art as represented by the cited references.

Accordingly, for the above reasons, the claims are deemed properly rejected and none are allowed.

***Correspondence***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Donna Jagoe whose telephone number is (571) 272-0576. The examiner can normally be reached on Monday through Friday from 8:00 A.M. - 4:30 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on (571) 272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Donna Jagoe /D. J./
Examiner
Art Unit 1614

January 18, 2009

/Ardin Marschel/
Supervisory Patent Examiner, Art Unit 1614